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Somatic *IDH1* mutation in a pituitary adenoma of a patient with Maffucci syndrome

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Abstract

Maffucci syndrome is a rare disease characterized by multiple enchondromas and soft-tissue hemangiomas. Additionally, neuroendocrine tumors including pituitary adenomas have been described in these patients. The underlying genetic etiology lies in somatic mosaicism of mutations in isocitrate dehydrogenase 1 *(IDH1)* or isocitrate dehydrogenase 2 *(IDH2)*. This report describes a patient with Maffucci syndrome who presented with intracranial tumors of the skull base and suprasellar region. The patient underwent resection of both intracranial tumors, revealing histopathological diagnoses of chondrosarcoma and pituitary adenoma. DNA sequencing of the tumors was performed to identify common *IDH1/2* mutations. Clinical, radiological, and biochemical assessments were performed. Genotypic studies used standard Sanger sequencing in conjunction with a target-specific peptide nucleic acid to detect *IDH1* mutations in tumor tissues. DNA sequencing demonstrated identical *IDH1* mutations (c.394C > T) in both tumors.

To the authors' knowledge, this report provides the first genetic evidence for the inclusion of pituitary adenomas among tumors characterizing Maffucci syndrome. In patients who are newly diagnosed with Maffucci syndrome, it is appropriate to monitor for development of pituitary pathology and neuroendocrine dysfunction.

Keywords

pituitary adenoma; isocitrate dehydrogenase; somatic mosaicism; Maffucci syndrome; oncology

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Zhuang, Hao, Zhang. Acquisition of data: Zhuang, Hao, Hong, Feng, Chittiboina, Zhang. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Zhuang, Hao, Hong, Feng, Zhang. Approved the final version of the manuscript on behalf of all authors: Zhuang. Administrative/technical/material support: Hao, Feng. Study supervision: Zhuang, Zhang.

MAFFUCCI syndrome and Ollier disease (OMIM 166000, ICD-10 Q78.4) are noninheritable conditions that are characterized by multiple enchondroma formation.[18] Unlike Ollier disease, patients with Maffucci syndrome also form soft-tissue hemangiomas. Patients typically present during the 1st decade of life with asymmetrical skeletal deformities and limb-length discrepancies, and may require surgery. Up to 40% of patients undergo malignant transformation of enchondromas into chondrosarcomas.[30] Recently, it was shown that individuals with Maffucci syndrome and Ollier disease harbor somatic mosaicism of mutations in isocitrate dehydrogenase 1 *(IDH1)* or isocitrate dehydrogenase 2 *(IDH2)*.[1]

Maffucci syndrome was originally characterized as enchondromatosis with hemangioma. However, additional tumors have been reported in these patients, including lymphangiomas, pancreatic adenocarcinomas, biliary adenocarcinomas, osteosarcomas, and mesenchymal ovarian tumors.[2,13,17,29] Additionally, intracranial tumors including astrocytomas, olfactory neuroblastomas, malignant chordomas, spindle cell hemangioendotheliomas, and pituitary adenomas have been described.[3,22,26] However, the only genetic evidence to demonstrate causality in these associations has been limited to an *IDH1*-mutated ovarian fibroma and an *IDH2*-mutated anaplastic astrocytoma in Ollier disease and Maffucci syndrome, respectively.[13,22]

We describe a patient with Maffucci syndrome who presented with 2 intracranial tumors: a jugular foramen chondrosarcoma and a pituitary adenoma. Both tumors exhibited identical *IDH1* mutations and represent the first genetic evidence of pituitary adenoma formation in Maffucci syndrome. Therefore, pituitary adenomas should be included among tumors in Maffucci syndrome that arise from somatic *IDH1/2* mutations.

METHODS

Study Oversight

This study was approved by the institutional review board of Beijing Tiantan Hospital of Capital Medical University (Beijing, China). The index patient provided written informed consent.

Immunohistochemistry

Routine H & E staining was performed on formalin-fixed tissue specimens to confirm histopathological diagnosis. Immunohistochemical staining was performed using the Bond automatic stainer and Bond ready-to-use antisynaptophysin antibody (both from Leica). Images were obtained at 200× magnification using a Nikon Eclipse Ci microscope with a Nikon DS-Fi2 camera.

DNA Extraction

DNA was extracted from formalin-fixed, paraffin-embedded tumor tissues using the QIAamp DNA FFPE Tissue Kit (Qiagen).

Polymerase Chain Reaction Conditions

Standard polymerase chain reaction (PCR) experiments contained 200–500 ng genomic DNA, 25 ml Taq 2× Master Mix (New England BioLabs), and 0.25 ml each of forward and reverse primers (100 mM) in a final volume of 50 ml. The PCR conditions were as follows: denaturation at 94°C for 15 minutes; followed by 40 cycles of 94°C for 30 seconds (denaturation), 55°C for 30 seconds (primer annealing), and 68°C for 60 seconds (extension), with a final extension step at 68°C for 5 minutes.

Peptide Nucleic Acid Design and PCR Conditions

The peptide nucleic acid (PNA) designed to detect wild-type *IDH1* was produced by PNA Bio. The sequence of the PNA was CATCATAGGTCGTCATGCTT-Lys-Lys. The 2 terminal lysine residues were added for improved solubility. The PCR experiments contained 200–500 ng genomic DNA, 25 ml Taq 2× Master Mix (New England BioLabs), 0.25 ml each of forward and reverse primers (100 mM), and 0.5 ml PNA (100 nM) in a final volume of 50 ml. The PCR conditions were as follows: denaturation at 94°C for 15 minutes; followed by 40 cycles of 94°C for 30 seconds (denaturation), 68°C for 60 seconds (PNA hybridization), 55°C for 30 seconds (primer annealing), and 72°C for 60 seconds (extension), with a final extension step at 72°C for 7 minutes.

Detection of R132 Mutation With Nested PCR and PNA Application

PCR amplification to introduce a site-directed mutation was initially performed, using 100 nM PNA as described above (forward primer ACCAACGACCAAGTCACCAA, reverse primer GTGTTGAGATGGACGCCTATT). PCR products were purified using QIAquick PCR columns (Qiagen). Subsequently, PCR amplification was repeated with the PNA, using nested primers (forward primer TGTGGAAATCACCAAATGGCAC, reverse primer TT GCTTAATGGGTGTAGATACCA). After purification, PCR products were analyzed by gel electrophoresis and subjected to Sanger sequencing for *IDH1* mutations, using the nested forward primer. The GenBank (National Center for Biotechnology Information) accession number for *IDH1* is NM_005896.2.

Case Report

History and Examination

A 28-year-old man presented with a 3-year history of voice hoarseness and dysphagia, and a 6-month history of left-sided blurred vision. His medical history was significant for development of multiple palpable nodular masses of the left hand beginning at 7 years of age (Fig. 1A), later accompanied by formation of subcutaneous blue, soft, nontender masses, diagnosed as hemangiomas on physical examination (Fig. 1A, inset). Radiographs of the left hand showed skeletal phalangeal malformation with calcific nodules and multiple enchondromas (Fig. 1B). Chest CT demonstrated enchondromas of the bilateral ribs and scapulae (Fig. 1C). Technetium-99m methylene diphosphonate whole-body bone scintigraphy revealed foci of intense tracer uptake, involving the right humerus, right ulna, right femur, right fibula, right tibia, left humerus, left radius, left hand, left femur, left fibula,

and left tibia (Fig. 1D). Based on these findings, the patient was diagnosed with Maffucci syndrome.

Neurological examination revealed left-sided deficits in hearing and gag reflex, bilateral temporal hemianopia, and decreased visual acuity (left eye 20/30; right eye 20/50). Brain MRI demonstrated 2 heterogeneously enhancing lesions, 1 in the left jugular foramen (Fig. 2A and B) and the other in the suprasellar region (Fig. 2C and D). The latter was suggestive of a pituitary macroadenoma. Serum prolactin (PRL), insulin-like growth factor-I, growth hormone (GH), cortisol, adrenocorticotropic hormone (ACTH), thyroid hormone, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were normal. A diagnosis of Maffucci syndrome associated with a nonfunctional pituitary adenoma was proposed.

Operation and Postoperative Course

A subtotal resection of the contrast-enhancing left jugular foramen lesion through a retrosigmoid approach was performed, resulting in significant improvement of the patient's dysphagia and auditory acuity. Histopathological review of the surgical specimen diagnosed a chondrosarcoma. Ten months after the first operation, the patient underwent gross-total resection of the suprasellar lesion via a subfrontal approach, revealing a diagnosis of pituitary adenoma. His postoperative recovery was uneventful other than transient polyuria. At the 2-year follow-up, the patient's voice hoarseness and visual acuity were significantly improved.

Pathological Examination and DNA Sequencing

Pathological examination of the jugular foramen specimen revealed a Grade II chondrosarcoma, characterized by moderate cellularity with occasional mitotic figures, cellular atypia, and increased muco-myxoid degeneration of chondroid matrix (Fig. 2E). Histopathological review of the pituitary adenoma demonstrated a highly cellular tumor with prominent monomorphism and loss of the normal reticulin meshwork (Fig. 2F). Immunohistochemical staining for synaptophysin confirmed this tumor to be of neuroendocrine origin (Fig. 2F, inset). Additional immunohistochemical investigation was negative for GH, PRL, LH, FSH, TSH, and ACTH (not shown).

Sanger sequencing of DNA from the pituitary adenoma revealed a c.394C > T mutation, a substitution of arginine at codon 132 with cysteine (R132C) (Fig. 3 center). To confirm these results, we performed repeat Sanger sequencing on significantly limited, remaining tissue, using nested PCR technique and a custom-designed PNA against the wild-type *IDH1* sequence (Fig. 3 lower). Use of PNA has been demonstrated to be an effective PCR clamp of wild-type sequences in samples where mutated cells are sparse.[6] Similarly, chondrosarcoma tissue was very limited but using the same techniques, a c.394C > T (R132C) mutation was detected (Fig. 3 upper).

Discussion

Although pituitary adenomas in patients with Maffucci syndrome have been previously described,[27] none established causality of pituitary adenoma in Maffucci syndrome through

analysis of *IDH1/2* mutations. Our report of a pituitary adenoma sharing an identical *IDH1* mutation with a chondrosarcoma in a patient with Maffucci syndrome supports the inclusion of pituitary adenomas among tumors characterizing Maffucci syndrome. Further investigations may reveal *IDH1/2* mutations in other tumor types reported to arise in patients with Maffucci syndrome.

Excluding the current study, 11 cases of pituitary adenoma in patients with Maffucci syndrome have been described and are shown in Table 1.[5,8,10,11,14,15,19,20,23,27,28] Among these, the majority (6/11) presented solely with visual field deficits, as did our patient. Further, none exhibited symptoms or evidence from immunohistochemical staining and/ or laboratory testing of hormonal abnormalities, indicative of a predominance of nonfunctional pituitary adenomas in this patient population. All patients except for 2 underwent resection, 1 of whom was diagnosed postmortem.[5] The other patient was treated with radiation only and was without recurrence at the 3-year follow-up.[19] There were 2 more cases of tumor recurrence within 3 years after surgical removal of the pituitary adenoma.[10,28] Further, similar to the patient described by Miki et al.,[20] there was little evidence of sellar enlargement upon review of imaging from our patient, which, although atypical for a pituitary adenoma, does not exclude its diagnosis.[25] Taken together, the clinical course of our patient is consistent with these previous studies, i.e., he presented solely with visual field deficits secondary to a nonfunctional pituitary adenoma and responded well to surgical treatment alone.

To our knowledge, the current case represents the first case of an *IDH1*-mutated pituitary adenoma. Balss et al. analyzed 23 samples of sporadic nonfunctional pituitary adenomas and failed to detect *IDH1* mutations, using direct DNA-sequencing techniques.[4] Similarly, Ikota et al. performed immunohistochemical staining for *IDH1* mutations in 42 pituitary adenoma samples, of which 2 exhibited 10%–30% positive immunoreactivity.[9] However, positive staining in these samples was confined to the cytoplasm. Because of this, the authors stated these findings should be considered negative, given the absence of concomitant nuclear staining, which is required for immunohistochemical diagnosis of *IDH1* mutations.

Maffucci syndrome was originally theorized as a condition of mesodermal dysplasia.[18] However, our study and Moriya et al.[22] question this theory because pituitary adenomas and astrocytomas arise from neuroectodermal tissues. Our finding of the same *IDH1* mutation in the chondrosarcoma (mesodermal origin) and pituitary adenoma (neuroectodermal origin) suggests *IDH1/2* mutations are early postzygotic events in Maffucci syndrome, occurring prior to gastrulation.[1,22] It is unclear which cell types are affected and harbor tumorigenic potential in Maffucci syndrome. Other endocrine tumors have been described in Maffucci syndrome, including thyroid adenoma, parathyroid adenoma, pheochromocytoma, and paraganglioma.[7,12,16,20,24] Further, endocrine tumor syndromes have been attributed to mutations in cellular metabolism genes, including succinate dehydrogenase *(SDH)*, hypoxia-inducible factor 2-alpha *(HIF2A)*, multiple endocrine neoplasia 1 *(MEN1)*, rearranged during transfection *(RET)*, and Von Hippel-Lindau *(VHL)*. *IDH1/2* mutations similarly alter metabolic pathways via mutant enzymatic production of the onco-metabolite, D-2-hydroxyglutarate, promoting development of low-grade gliomas and hematopoietic malignancies.[21] As this report suggests, *IDH1/2* mutations in Maffucci syndrome may affect

cells beyond mesenchymal lineage, including neuroectodermal cells that may form tumors. *IDH1/2* sequencing of more neuroendocrine tumors from patients with Maffucci syndrome will be re quired to answer this question.

In summary, we provide sufficient genetic evidence for the inclusion of pituitary adenomas among tumors that arise from *IDH1* mutation mosaicism in Maffucci syndrome. Because *IDH1/2* mutations in Maffucci syndrome predispose cells to, rather than incite, tumorigenesis, it is yet to be seen whether *IDH1* and *IDH2* represent cancer-susceptibility genes, similar to *SDH*, *MEN1*, and *RET*.

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ABBREVIATIONS

ACTH	adrenocorticotropic hormone
FSH	follicle-stimulating hormone
GH	growth hormone
IDH1	isocitrate dehydrogenase 1
IDH2	isocitrate dehydrogenase 2
LH	luteinizing hormone
MEN1	multiple endocrine neoplasia 1
PCR	polymerase chain reaction
NPA	peptide nucleic acid
PRL	prolactin
RET	rearranged during transfection
SDH	succinate dehydrogenase
TSH	thyroid-stimulating hormone

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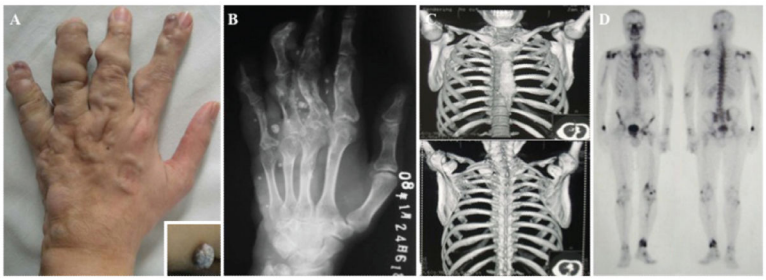

Fig. 1.

Clinical presentation of index patient. A photograph of the index patient's left hand is shown **(a)**. Numerous palpable nodules were evident, which had been present since childhood. Multiple hemangiomas spread throughout his body were found, including his right buttock **(inset)**. A radiograph of the left hand showed calcific nodules and lytic lesions of the phalanges, characteristic of enchondromas **(b)**. 3D anterior *(upper panel)* and posterior *(lower panel)* reconstruction of a chest CT showed additional osseous lytic lesions **(c)**. Whole-body bone scintigraphy revealed multiple areas of increased radiotracer uptake, suggestive of enchondromatosis **(d)**. Figure is available in color online only.

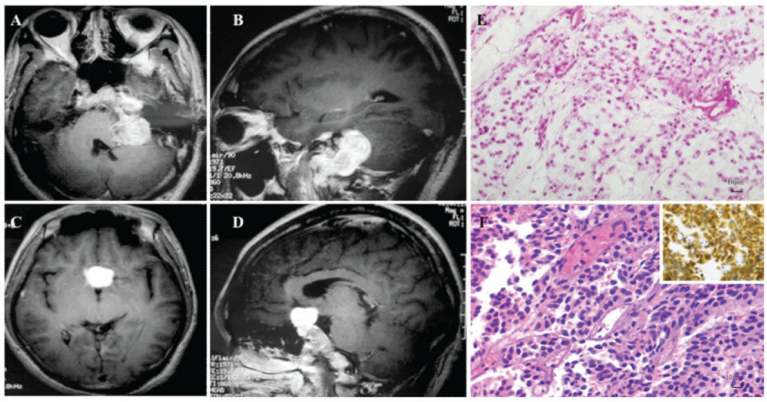

Fig. 2.

Radiographic and histological tumor characteristics. Axial **(a)** and sagittal **(b)** sections of a T1-weighted MRI study obtained after contrast administration demonstrated a heterogeneously enhancing lesion encasing the left jugular foramen of the skull base. Axial **(c)** and sagittal **(d)** T1-weighted MRI studies obtained after contrast administration showed a strongly enhancing suprasellar mass. A representative image of the H & E–stained sample (original magnification ×200), excised from the jugular foramen, exhibited increased cellular atypia amid a degenerative muco-myxoid chondroid matrix, suggestive of a Grade II chondrosarcoma **(e)**. An H & E–stained photomicrograph (original magnification ×200) of tissue from the suprasellar mass showed monomorphic cellularity and disorganized reticulin meshwork **(F)**. There was prominent positive staining for the neuroendocrine marker, synaptophysin, confirming neuroendocrine origin and diagnostic of pituitary adenoma **(inset)**. Figure is available in color online only.

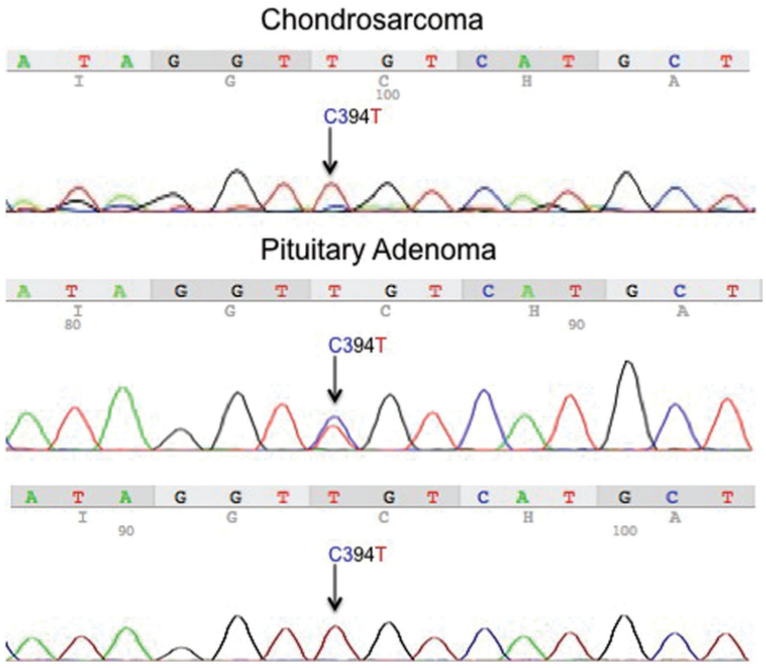

Fig. 3.

DNA sequencing of tumor *IDH1*. Sanger sequencing of DNA extracted from the pituitary adenoma revealed a c.394C > T (R132C) mutation of *IDH1* **(center)**. Repeat sequencing was performed on DNA derived from remaining paraffin-embedded tissue, using PNA and nested PCR technique, which confirmed previous results **(lower)**. Using the same methodology of PNA and nested PCR, the same c.394C > T mutation was found in DNA from the chondrosarcoma tissue **(upper)**. Figure is available in color online only.

table 1

previously published cases of pituitary adenomas in patients with maffucci syndrome

Authors & Year	Clinical Presentation	Features of Histological Subtype
Kuzma & King, 1948	Asymptomatic	Not performed
Baradnay et al., 1960	Incidental finding postmortem	Chromophobic staining
Jingu et al., 1973	Visual field defects	Chromophobic staining
Schnall & Genuth, 1976	Visual field defects	Chromophobic staining
Marymont et al., 1987	Incidental finding	Not performed
Miki et al., 1987	Visual field defects	Chromophobic staining
Howie & Davidson, 1988	Visual field defects	Basophilic staining
Kitamura et al., 2006	Cluster headaches	Normal endocrine laboratory results
Ruivo & Antunes, 2009	Visual field deficits	Normal endocrine laboratory results
Imai et al., 2012	Visual field deficits	Not specifed
Ono et al., 2012	Not specified	Not specified